

Prevention of recurrent thrombosis in the antiphospholipid antibody syndrome: how long and how high with oral anticoagulant therapy?

Unravelling the uncertainties

THE ANTIPHOSPHOLIPID ANTIBODY SYNDROME is an autoimmune disease that commonly presents with either venous thromboembolism (VTE) (deep vein thrombosis, pulmonary embolism), arterial thrombosis (ischaemic stroke, coronary thrombosis, peripheral arterial occlusion) or unexplained fetal loss. A high index of suspicion for the diagnosis is raised in patients with unusual thrombosis, those without obvious risk factors, or those who experience recurrent events. The diagnosis is based on presentation with one of the above clinical criteria and detection in the laboratory of persistent antiphospholipid antibodies. Clinically relevant antiphospholipid antibodies are identified by either functional coagulation assays (lupus anticoagulant) or immunoassays (anticardiolipin antibody, β_2 -glycoprotein-1 antibody).^{1,2} When considering the diagnosis of the antiphospholipid antibody syndrome, it is important to perform both clotting and serological tests, as they are concurrently positive in 50% of unequivocal cases.³ The detection of a lupus anticoagulant and/or medium- to high-titre IgG antiphospholipid antibodies is associated with an approximately 10-fold increase in risk of VTE.^{4,5} Unlike the treatment for other autoimmune disorders, anticoagulation rather than immunosuppression is the mainstay of treatment.¹⁻³

Significantly elevated levels of antiphospholipid antibodies are detected in up to 20% of patients with VTE, compared with only 2% of healthy adults.⁶ This means that clinicians will be frequently asked to make decisions based on positive antibody test results. With about 40 000 tests for thrombophilia performed in Australia each year,⁷ the question arises as to the impact of testing for antiphospholipid antibodies in clinical practice. Why are we performing these tests?

Up to now the reason has been twofold. Firstly, there is a perception that there is a high risk of recurrent thrombotic episodes, and even death, when anticoagulation treatment is stopped in people with antiphospholipid antibodies. Several retrospective studies have suggested that treatment with warfarin should be continued for at least 12 months, if not longer or lifelong, as up to 70% of patients will have recurrent events without ongoing treatment.^{8,9}

For patients with arterial occlusion, particularly those without other atherosclerotic risk factors (eg, smoking, diabetes, hyperlipidaemia, hypertension), recurrence of thrombosis from significant levels of antiphospholipid antibodies would be catastrophic. For such patients, anticoagulation is usually continued. For patients with VTE and no obvious risk factors, testing of antibody levels may help to resolve the current uncertainty about the optimal duration of anticoagulation treatment and may even help to determine whether anticoagulation should be stopped at all. In a multicentre study, 412 patients were prospectively followed

after a first episode of VTE: within 4 years after ceasing warfarin, 29% of patients with IgG anticardiolipin antibodies had experienced further events, compared with 14% without antibodies.⁶ However, maintaining people on long-term warfarin therapy carries the inevitable risk of serious haemorrhage (1.1 events/100 patient-years) and anticoagulant-related death (0.25 deaths/100 patient years).¹⁰ If we had further data on the optimal duration of anticoagulation treatment, we would be in a better position to discuss with patients the risk versus benefit of ongoing treatment.

The second reason for determining the presence of antiphospholipid antibodies is that it assists in deciding the optimal intensity of anticoagulation treatment. There is evidence from retrospective case series that recurrence of thrombotic episodes can occur even with moderate-intensity warfarin therapy (target international normalised ratio [INR], 2.0–3.0) when compared with higher-intensity therapy (target INR, 3.0–4.5).^{8,9} However, this information comes from specialised expert clinics for high-risk patients, and to generalise the findings to a large number of VTE patients without better evidence is problematic. The cost of having a higher INR (3.0–4.4 rather than 2.0–2.9) is the doubling of the risk of any bleeding event.¹⁰

A recent prospective randomised controlled trial on the efficacy and safety of high-intensity warfarin treatment (target INR, 3.0–4.0) versus standard-intensity treatment (target INR, 2.0–3.0) in 114 patients with arterial thrombosis and VTE with antiphospholipid antibodies attempted to address this uncertainty.¹¹ The results of the trial showed that there was no difference in the rates of recurrent thrombosis and bleeding between the two groups. Although the confidence intervals were wide because the number of events was small, the study does give some guidance regarding treatment decisions for the majority of patients with thrombosis and antiphospholipid antibodies. However, there are several caveats:

- Patients were included after already receiving warfarin for variable periods of time, and only a third of patients were allocated to one of the trial groups within 6 months of thromboembolism. This means that patients who were at highest risk of recurrence or bleeding while on warfarin were excluded;
- Patients who already had recurrent thrombosis while receiving warfarin with a target INR > 2.0 were specifically excluded;
- Control of INR range was supervised by expert clinic staff, who kept INRs within range 70% of the time for the standard-intensity arm and 40% of the time for the high-intensity arm. Most of the patients out of the INR target range in the high-intensity group were below the therapeutic range. Whether this degree of control for a given target INR is achieved in everyday practice is uncertain and needs

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further validation. It highlights the difficulty of maintaining a narrow therapeutic target INR range with warfarin despite the best intentions.

Given the limitations of the published studies, the clinician is still faced with uncertainty in dealing with patients with thrombosis and antiphospholipid antibodies. For most people with thrombosis and antiphospholipid antibodies, long-term standard-intensity warfarin with a target range INR 2.0–3.0 may be appropriate. However, there will still be patients with extensive or unusual thrombosis for whom higher-intensity anticoagulation treatment could be considered. This situation applies particularly to people in whom recurrence may be threatening to life, limb or organ, particularly when no other recognised risk factor for either VTE or atherothrombosis can be removed or modified. To reliably answer the question of how to manage patients with thrombosis and a significant level of antiphospholipid antibodies would require an inception cohort study, with patients randomised at diagnosis to different intensities of anticoagulation treatment.

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